Reviewer's report

Title: Characterizing measles transmission in India: a dynamic modeling study using verbal autopsy data

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Reviewer: James Wood

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This interesting study compares predictions from a transmission model of measles with Indian mortality data in order to estimate case-fatality rates in this context and the impact of recent immunisation activities on deaths due to measles in India. However, I have concerns about the inadequacy of detail on the model in the paper and the approach taken for informing parameter choices. I elaborate on these issues below:

Model detail: This paper provides very little detail on the structure of the model and only limited information for on how specific scenarios are conducted. While the paper refers to an earlier published paper for details, even within that article model details are glossed over. For instance it appears as if the partial differential equations are approximated through a "realistic-age-structured" approach whereby ageing happens at the end of each year but this is not explicitly described. One reason for this detail being of interest is that such an approach leads to annual oscillation in modelled incidence, which is of relevance to the analysis of periodicity described here.

I also note that essentially no intermediate results from the model are provided. No graphs of incidence over time or by age are provided on the approach to equilibrium or at equilibrium either. I appreciate that a number of results are based on running thousands of simulations but even the range of variation of model output at equilibrium within a 3-year period would be of interest. Only the variation in total case numbers is shown.

In addition, the use of other data is not transparent - how was the Indian population data used? Presumably to inform initial population sizes and mortality rates but the details of that should have been provided. Also, the denominator data for the deaths should have been provided at least in summary form. The contact matrix is presumably as noted in reference 14 but this is not mentioned within this paper.
Calibration approach: While I have concerns about the lack of detail on the model, it is the area of calibration that I think is weakest in the paper. Ideally for calibration you have accurate information on incidence in both time and age. In developed settings, usually population seroprevalence surveys are available to inform estimates in relation to this but in settings such as India these are generally not available. Therefore the authors attempt to use the mortality data to help refine estimates of the basic reproduction number and forcing. One immediate issue with this is that the authors also hope to estimate a case-fatality rate and therefore only the relative changes in mortality can be used to inform estimates of the other parameters.

The authors use Fourier analysis to determine the strongest periods in the mortality data (aggregated and separately in the two highlighted states). The transmission model was run to equilibrium post-vaccination with coverage set at 2000–2003 levels and then coherence of the case time series at equilibrium was compared with mortality time series at each of the selected periods and is also via a pooled estimate. I have 3 main issues with this approach:

1. The mortality time series is relatively short at 4 years of data and even at the all-India level, patterns in the data are not completely clear. At a state level, particularly in Bihar, I think it would difficult to show that the data shown is non-Poisson (i.e. that it has any periodic structure is not self-evident just from the data). As such, I feel that the approach of using patterns in this data as a calibration tool is doubtful just on observation of the data.

2. It's unclear to me why a comparison of post-vaccination equilibrium model behaviour with the 2000–2003 mortality data is reasonable. Yes, the post-vaccination equilibrium behaviour will be more stable than pre-equilibrium model behaviour but the mortality data does not reflect a situation at equilibrium. Vaccination coverage is changing, birth rates are changing and as observed in Hempel, 2015. DOI: 10.1098/rsif.2015.0024, relatively small changes to birth rates can cause major transitions in measles epidemic cycles.

3. As I understand it, the authors are using a seasonally forced model of measles. These models are known to produce a variety of periodic behaviour and even chaotic behaviour. As such, even if the match between the simulations and the mortality data was excellent, the accuracy of parameter estimates would remain unclear (as the model might produce quite different trajectories for only small changes in these values). Thus, whether the strength of the coherence as determined here is really useful in refining parameter values is unclear to me.
I also note that when one looks at the plots of coherence against parameter values and the estimated case fatality rate, these do not reveal any simple structure in this relationship. My take on this is that data is not very informative about these values. I'm also concerned as to whether the approach by which the model is solved (ageing at the end of each year) leads to additional annual forcing within the modelled data that affects these coherence estimates.

As such, I think much of the analysis presented is not necessarily very helpful towards the endpoint of estimating case fatality rates. These are already rather constrained just by the range of R0 values used in this analysis and I think it would be at least a better starting point to simply present the case-fatality rates derived from applying this range and then, if the issues with coherence noted above can be sorted out, to apply this as a secondary analysis in an effort to refine these estimates.

A final minor point. The authors should include A BenYishay and K Kranker. All-Cause Mortality Reductions from Measles Catchup Campaigns in Africa J. Human Resources 2015 50:516-547; doi:10.3368/jhr.50.2.516 as part of their discussion of measles mortality estimates and the impact of SIAs.

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If not, please specify what is required in your comments to the authors.

No

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